Defining new standards of care for men with prostate cancer

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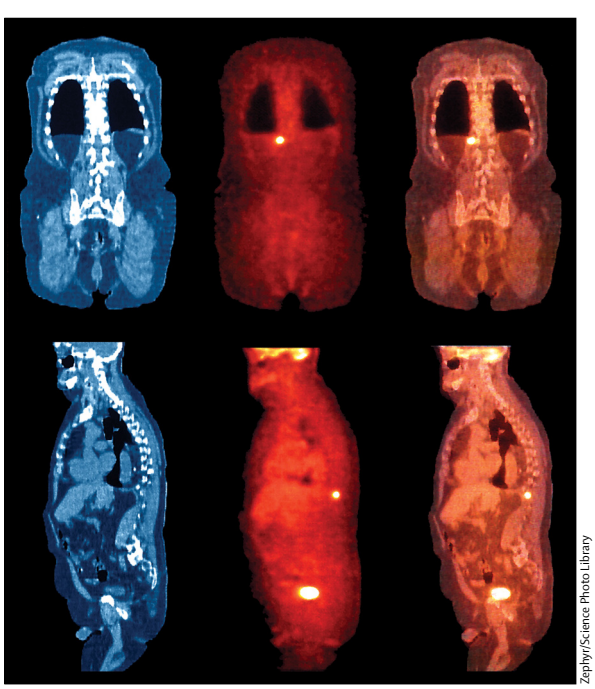
Improving the outcomes of medical or surgical castration for men with prostate cancer has been an elusive goal since the approach was first reported in the 1940s.[1] However, this situation changed at the annual American Society of Clinical Oncology meeting in 2014, when results reported from the ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease (CHAARTED) showed that addition of six cycles of docetaxel to standard of care (testosterone lowering hormone therapy) prolonged the survival of men with metastatic disease at the time of diagnosis relative to treatment with hormones alone.[2,3] The result contrasted with a trial of similar design, GETUG-AFU 15, that did not show a survival benefit.[4]

In *The Lancet*, Nicholas James and colleagues[5] report on the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study, a multinational trial of unparalleled scope and size designed to establish new standards of care for prostate cancer patients starting first-line hormone therapy. The report includes 2962 men with high-risk localised, node-only disease, and metastatic disease that was newly diagnosed or that relapsed after local therapy, who were randomised to one of four treatment groups: standard of care (SOC) alone, standard of care plus zoledronic acid (SOC + ZA), standard of care plus docetaxel (SOC + Doc), or standard of care plus zoledronic acid plus docetaxel (SOC + ZA + Doc).

Overall, relative to SOC alone, SOC + Doc reduced mortality by 22% (hazard ratio 0·78 [95% CI 0·66–0·93]), prolonged median overall survival by 10 months (81 months *vs* 71 months), and increased absolute 5-year survival by 8% (63% *vs* 55%). For the subset of patients with metastatic disease, the relative reduction in mortality was 24% (hazard ratio 0·76 [95% CI 0·62–0·92]), median survival increased by 15 months (60 months *vs* 45 months), and absolute 5-year survival increased by 11% (50% *vs* 39%). Favourable effects on failure-free survival—defined as time from randomisation to evidence of at least one of the following: biochemical failure; local, nodal, or metastatic progression; or death from prostate cancer—were also reported. No survival benefit, prolongation of failure-free survival, or reduction in the frequency of skeletal-related events was seen for adding zoledronic acid to either SOC alone or SOC + Doc. However, the addition of docetaxel did delay the time to the first skeletal-related event. Safety and tolerance were as anticipated for docetaxel and, although the frequency of grade 3 or higher adverse events was increased in the first 6 months, the overall frequencies at 1 year were similar for the docetaxel and non-docetaxel treatment groups.

James and colleagues' results[5] provide further unequivocal level 1 evidence of a meaningful clinical benefit for early docetaxel relative to the potential risks and harms, leading the study authors to conclude that the "standard of care should be updated to include docetaxel chemotherapy in suitable patients with metastatic disease", similar to the group shown to benefit in CHAARTED, and that it "may be considered for men with high-risk non-metastatic" disease. Adding zoledronic acid to standard of care was not recommended.[5]

Based on the results of STAMPEDE and CHAARTED, should all men with newly diagnosed or recurrent metastatic disease receive chemotherapy? No. Even though over 100 sites participated in STAMPEDE and accrual was not restricted to academic high volume centres, the patients enrolled were not representative of a general prostate cancer population in that 97% had no cardiovascular history, 99% no cerebrovascular history, 100% no history of congestive heart failure, and over 90% no history of diabetes. Few had performance



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status 1 or greater. In a Canadian study,[6] use of docetaxel in patients with metastatic castration-resistant prostate cancer by the same physicians at the same institution, at the same dose and schedule, off-protocol resulted in higher morbidity and inferior outcomes relative to patients treated on-protocol strictly on the basis of demographics. The non-castrate metastatic disease state includes patients with one or two lesions, 20 or more lesions, bone marrow entirely replaced by tumour, and those with or without symptoms. Tolerance and safety are unlikely to be the same in the two settings. The non-castrate metastatic state also includes patients metastatic at diagnosis and those who develop metastases after failing local therapy for whom median survival times are inherently longer,[7] and, although there was no evidence of heterogeneity across subgroups, patients older than 70 years did not appear to benefit.[5]

Hidden factors might have affected survival outcomes in favour of the groups treated with chemotherapy relative to those not treated with chemotherapy. Reported are the specific therapies received and how long after a failure event was documented. Most failures were biochemical, and about 80% of patients in each group received a new treatment within 6 months. Most treatments were not life prolonging. During the course of STAMPEDE,[5] four additional therapies proven to prolong life in metastatic castration-resistant prostate cancer became available, which were also given at a similar time and frequency to the four treatment groups after the failure event. Not surprisingly, a higher percentage of patients in the SOC alone and SOC + ZA groups received docetaxel and a lower percentage abiraterone, enzalutamide, or cabazitaxel relative to the SOC + Doc and SOC + Doc + ZA groups.

A concern is that 40% of patients in the non-docetaxel containing groups had not received docetaxel or any other life-prolonging therapy. These imbalances could have affected the survival outcome in favour of early chemotherapy. Notable here is that the relative percentage of patients receiving a newly approved life-prolonging therapy and docetaxel in the SOC + Doc group relative to the standard of care groups in CHAARTED which showed a survival benefit was 25% and 50% greater than GETUG-AFU 15, a trial that largely accrued before these therapies were available and showed no survival benefit.[7] Showing the post-failure survival of the four groups, although not definitive, could shed some light. An additional question that has not been formally addressed by either STAMPEDE or CHAARTED, and which remains open, is whether chemotherapy given early versus chemotherapy given later at the time of failure or progression would have produced similar overall survival times.[8]

For patients with non-metastatic disease, the hazard ratio for the reduction in mortality was similar to that observed in metastatic patients, but the results are not definitive due to the short follow-up and insufficient number of events. An important amendment to the STAMPEDE trial in 2011 was to require radiation therapy to the primary tumour, previously shown to improve survival relative to standard of care hormone therapy or radiation therapy alone.[9,10] For these patients, failure rates and overall prostate cancer-specific death rates are lower than for men with metastatic disease and the net benefit of early chemotherapy is less certain. For those not at risk of dying of prostate cancer, or who have tumours that can be successfully treated with standard of care hormones and local therapy alone, or who have tumours that are insensitive to docetaxel, any chemotherapy is overtreatment.

Additionally, in *The Lancet Oncology*, Claire Vale and colleagues[11] have reported a meta-analysis that considers ongoing trials that might affect outcomes, based solely on completed studies. The conclusions for metastatic (M1) disease were based on the results of CHAARTED,[3] GETUG-AFU 15,[4] and STAMPEDE[5] representing 2992 (93%) of the 3206 patients enrolled in the relevant trials. The combined analysis showed an absolute 9% (95% CI 5–14) improvement in survival at 4 years, and makes it essential that the role of docetaxel in combination with hormones be discussed. However, for an individual patient careful consideration must be given to comorbidities that might compromise tolerance and the ability to give chemotherapy safely. For patients with locally advanced (M0) disease, failure-free survival was consistently prolonged with docetaxel (hazard ratio 0·70 [95% CI 0·61–0·81]) but an effect on survival has not been firmly established (0·87 [0·69–1·09]). For these patients, prognostic models that can define the risk of developing metastatic disease, symptoms, and death from prostate cancer, and, for all cohorts, biomarkers that predict which tumours are likely to be sensitive to docetaxel, are needed to better inform management for the individual patient. Participation in protocols designed to address these questions is strongly encouraged.

Overall, the STAMPEDE results[5] mandate a discussion of the proven benefit of early chemotherapy in combination with standard of care hormone therapy for men with metastatic disease at diagnosis, or who develop metastatic disease after local therapy with consideration to patient factors that might affect tolerance and safety. Longer follow-up, as noted by the authors, is required before the benefit-to-risk ratio is definitively established in earlier disease states. Needed now is a biological understanding of which tumours will be sensitive to docetaxel, which will not, and which might be more responsive to a next-generation agent directed to the androgen receptor or androgen receptor signalling, or another class of drug. Doing so will spare patients potentially ineffective treatment. Equally important is the drug assessment paradigm established by STAMPEDE that enables new systemic and combined modality approaches to be assessed at a more rapid pace than could have been achieved with more traditional research designs.[12] The trial has already, and will continue to provide, a treasure trove of data that directly affects the management and outcomes for men with different states of prostate cancer.

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Cardiac gene therapy: a call for basic methods development

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In 1995, when I entered the specialty of cardiac gene therapy, the principal limitation was the inability to reliably transfer genes to the cardiac ventricles. Soon after that time, a series of angiogenesis gene therapy clinical trials did not show efficacy in randomised testing.[1,2] Investigation of the delivery methods used in those studies verified that insufficient gene transfer was a significant factor.[3] In 2016, with the publication of Barry Greenberg and colleagues' study,[4] CUPID 2, we see that a principal limitation to cardiac gene therapy continues to be the inability to reliably transfer genes to the cardiac ventricles. In their randomised, multinational, double-blind, placebo-controlled, phase 2b trial, Greenberg and colleagues compared 121 patients with heart failure and reduced ejection fraction who received an intracoronary infusion of adeno-associated virus 1 (AAV1) encoding the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase gene with 122 patients who received placebo. In a detailed analysis of time to recurrent heart failure events (primary endpoint), time